

Blau-Jabs Syndrome in a Tertiary Ophthalmologic Center

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ABSTRACT: In a prospective case series of patients with Blau-Jabs syndrome (BJS) conducted in the Ophthalmology Department/Federal University of Sao Paulo, seven patients with clinical and ophthalmologic manifestations of the disease and a positive genetic test result for the presence of a mutation in the *CARD15/NOD2* gene were followed for a minimal period of 1 year. All patients had uveitis, five had nummular corneal subepithelial opacities, and four had multifocal choroiditis. Oral prednisolone was administered to all patients; inflammation was controlled in six patients with at least one immunosuppressive drug. Infliximab (Remicade; Janssen Pharmaceuticals, Beerse, Belgium) and etanercept (Enbrel; Amgen, Thousand Oaks, CA) were used to treat two cases refractory to the anti-inflammatory drugs. A subconjunctival dexamethasone implant (Ozurdex; Allergan, Irvine, CA) and a periocular injection of triamcinolone were used in one case to achieve inflammation control. Six patients achieved a visual acuity of 20/25 or better. The authors conclude that periocular treatment with steroid injections might be effective adjuvant therapy to control ocular inflammation.

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INTRODUCTION

Blau-Jabs syndrome (BJS), first described simultaneously by Blau and Jabs in 1985, is an autosomal dominant chronic inflammatory syndrome defined by early onset of noncaseating granulomatous dermatitis, arthritis, and uveitis.^{1,2} The disease is rare, with fewer than 200 cases reported by 2015, most of them with onset in white patients younger than 4 years of age.³⁻⁵ The main differential diagnosis is sarcoidosis.^{4,5} BJS is distinguished from sarcoidosis by the absence of pulmonary involvement and adenopathies, the arthritis pattern, and familial inheritance⁶ related to the *CARD15* (caspase activation and recruitment domain [CARD] family, member 15)/*NOD2* (nucleotide-binding oligomerization domain-containing protein 2) gene on chromosome 16q12, identified in 2001.^{4,5,7} This gene also is involved in Crohn's disease.⁷

Anterior, posterior, and diffuse uveitis, and corneal opacities might occur.⁷⁻⁹ Ocular involvement is described as the most relevant morbidity of BJS.³ Uveitis generally is later and bilateral and might lead to low visual acuity (VA) in up to 46% of cases.^{7,10-12} Other ocular lesions are conjunctival nodules and multifocal choroidal and granulomatous optic disc lesions.^{10,12} Most cases are treated with oral steroids;^{5,13} many also need immunosuppressive agents. Recurrences are common.⁷ Biologic anti-cytokine agents have been suggested to be promising treatments in refractory cases.^{3,14}

The goals of the current study were to increase the information in the literature about the demographic, clinical ophthalmological and systemic findings, and the beneficial treatments for this rare disease.

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Figure 1. Case 3. Anterior biomicroscopy image of an eye with uveitis in Blau-Jabs syndrome. Nummular corneal opacities and posterior synechiae are seen.

PATIENTS AND METHODS

In a prospective study, seven patients diagnosed with BJS in a tertiary care ophthalmology department of the Federal University of São Paulo, Brazil, from 2014 to 2015 were consecutively selected and included. Investigational review board approval was obtained for this study. The diagnostic criteria were the clinical and ophthalmologic manifestations and a mutation in the *CARD15/NOD2* gene identified by genetic testing. All patients had a follow-up of at least 1 year and underwent systemic and ophthalmologic examinations and genetics evaluations.

RESULTS

From 2014 to 2015, seven patients with BJS were diagnosed, all of whom had a positive genetic test for BJS (presence of a *CARD15/NOD2* mutation). Five (71%) patients were female, and the average age was 18.5 years (range: 10 years to 41 years). All

patients had granulomatous uveitis, five had pan-uveitis, and two had anterior uveitis. Five (71%) patients had nummular corneal subepithelial opacities (Figure 1) and four (57%) had multifocal chorioiditis. Table 1 shows the clinical presentations, treatment, and complications.

All patients presented with arthritis; only one did not have a skin rash. Two (29%) patients also had chronic fever and one (14%) had a history of diarrhea. All patients were treated with oral prednisone, six (86%) used at least one immunosuppressive drug to control inflammation — specifically, methotrexate (83%) and cyclosporine (40%). In two refractory cases, biologic drugs were introduced — infliximab (Remicade; Janssen Pharmaceuticals, Beerse, Belgium) (Case 1) and etanercept (Enbrel; Amgen, Thousand Oaks, CA) (Case 5). In Case 1, despite treatment with steroid pulse therapy and immunosuppressive agents, the patient presented with refractory anterior uveitis (Figures 2A and

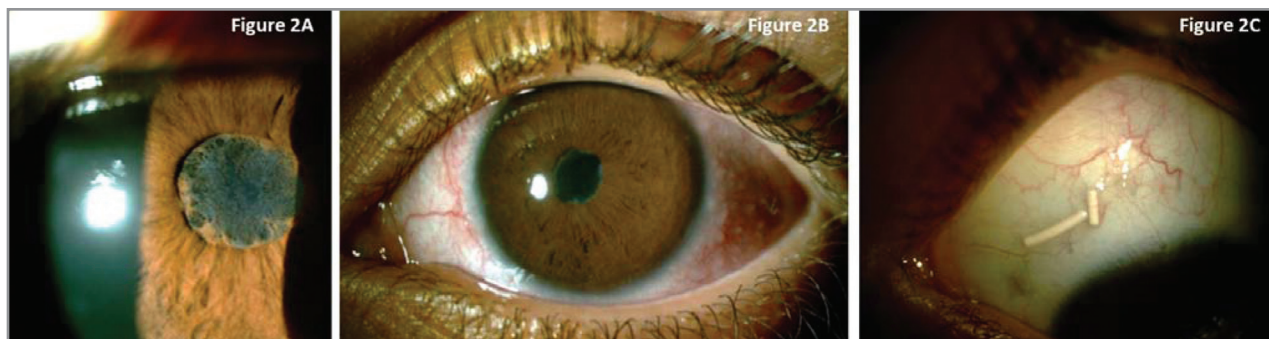


Figure 2. Case 1. Anterior biomicroscopy image of an eye with uveitis in Blau-Jabs syndrome. (A) Posterior synechiae with a pupillary membrane. (B) Granulomatous conjunctivitis with hyperemia, nodules, and posterior synechiae. (C) A dexamethasone subconjunctival implant helped control the inflammatory activity.

2B). Treatment with a subconjunctival dexamethasone implant (Ozurdex; Allergan, Irvine, CA) in the left eye and a periocular triamcinolone injection in the right eye was added to control the inflammation (Figure 2C). The ocular hypertension that developed after the subconjunctival implant in the left eye was controlled with topical timolol 0.5%. No other patient developed ocular hypertension during the study period.

The most common treatment-related complication was posterior synechiae in 86%, followed by posterior subcapsular cataract (29%), macular edema (29%), and corneal band keratopathy (14%). One patient did not have any complications. After treatment, six (86%) patients had a VA of 20/25 or better. No surgical treatment for cataract and band keratopathy was required at this moment. The low VA persisted in one patient (Case 4) likely because of dense bilateral corneal band keratopathy.

DISCUSSION

BJS is an autosomal dominant disease caused by a mutation in the caspase recruitment domain gene *CARD15/NOD2*.^{3,12} The disease classically presents in early childhood and is characterized by granulomatous dermatitis, arthritis, and uveitis.^{4,13,15} The current patients were older than those reported in the literature probably due to the difficulty in diagnosing the disease, both because of its rarity and the need for confirmatory genetic testing. The literature states that uveitis generally is present in 60% to 80% of patients 2 years to 4 years of age.¹³ All of the current patients had uveitis, possibly because the study was performed in a tertiary ophthalmological center.

Rash, usually the first sign to appear in BJS,^{13,15} most often is an erythematous maculo/micropapular fine scaly rash on the trunk and extremities.^{5,13,16}

The arthritis in BJS manifests as polyarticular synovitis and tenosynovitis, usually in the wrists, knees, ankles, and proximal interphalangeal joints (PIP) of the hands.^{4,5,13} All current patients presented with arthritis and only one did not have the skin rash. A characteristic manifestation (ie, camptodactyly) is contracture of the PIP joints relatively early in the disease course and out of proportion to the degree of synovitis.^{5,13,15} Other systemic manifestations seen in our series were chronic fever and diarrhea.

Ocular involvement occurs in 80% to 85% of patients and is typically a chronic bilateral granulomatous iridocyclitis with posterior uveitis.^{5,13} The ocular inflammation might evolve to severe panuveitis with multifocal choroiditis.^{5,13} In the current series, all patients had granulomatous uveitis, most with panuveitis, but some with anterior uveitis and four with multifocal choroiditis.

Corneal opacities were first described by Charavérian et al. in 1993. Since then, other authors have described the same alterations as small, evanescent, ovoid corneal subepithelial, and stromal opacities.^{7,9} Corneal opacities have been described in other *CARD15/NOD2*-associated diseases such as Crohn's disease, but they are usually epithelial and subepithelial and located in the peripheral and juxtalimbal cornea and have a partial response to corticoid therapy.¹⁷ In the current patients, 71% had nummular opacities that persisted and increased in number in proportion to the degree of inflammation. Thus, they helped in the diagnosis of disease activity and in monitoring the treatment response.

Other possible ocular findings are: epiretinal membranes, granulomatous discs, papilledema, ischemic optic neuropathy, retinal vasculitis, progressive subretinal fibrosis, and fourth nerve palsy.^{2,3,13,18} Ocular involvement in BJS has been reported to complicate the disease in more than a third of

TABLE 1
Clinical Ocular and Systemic Presentations and Complications

Case	Gender	Age (Years)	Ocular Findings	Systemic Findings	Treatment	Complications
1	Male	10	Granulomatous panuveitis with nummular corneal subepithelial opacities, conjunctival nodules, and multifocal choroiditis OU	Arthritis, chronic fever, skin rash, diarrhea	Pulse therapy with methylprednisolone, oral prednisone, methotrexate, and infliximab + periocular triamcinolone acetate OD and subconjunctival dexamethasone implant OS	Side effects of mycophenolate, posterior subcapsular cataract, macular edema, posterior synechiae and ocular hypertension
2	Female	12	Granulomatous panuveitis, panuveitis with nummular corneal subepithelial opacities OU	Skin rash, arthritis	Oral prednisone, methotrexate, cyclosporine	Posterior synechiae
3	Male	10	Granulomatous anterior uveitis with nummular corneal subepithelial opacities OU	Chronic fever, skin rash, arthritis	Oral prednisone, methotrexate	Posterior synechiae
4	Female	28	Recurrent granulomatous panuveitis with multifocal choroiditis OU	Skin rash, arthritis	Oral prednisone, cyclosporine	Corneal band keratopathy and posterior synechiae
5	Female	21	Recurrent granulomatous panuveitis with nummular corneal opacities, multifocal choroiditis, granulomatous discs in OU	Skin rash, arthritis	Oral prednisone, etanercept, methotrexate	None
6	Female	41	Recurrent granulomatous panuveitis with multifocal choroiditis OU	Skin rash, arthritis	Oral prednisone	Posterior subcapsular cataract, posterior synechiae and macular edema OU
7	Female	10	Anterior granulomatous uveitis with nummular corneal opacities, conjunctival nodules OU	Arthritis	Oral prednisone, methotrexate	Posterior synechiae

OU = both eyes; OS = left eye; OD = right eye

cases, most often with posterior synechiae, band keratopathy, cataract, glaucoma, cystoid macular edema, optic atrophy, and retinal detachment.^{1-3,10-13,18} In a study of 22 patients, 16% presented with blindness and 11% with moderate visual impairment.¹³ The current results agreed with those reported in the literature, with the main complications being posterior synechiae, posterior subcapsular cataracts, macular edema, and corneal band keratopathy.

Despite the characteristic clinical findings, the final diagnosis is based on the results of genetic

testing. BJS is associated with different *CARD15/NOD2* mutations on chromosome16q12.^{4,13} The effects of the *CARD15/NOD2* mutations in BJS are not totally understood; some authors believe that mycobacterial components might trigger granulomatous autoinflammation.⁵

Although there is no consensus about the optimal treatment for patients with BJS, they require continuous follow-up.^{5,13} More than two-thirds of patients with BJS received medical therapy, often high-dose steroids, especially in the acute stag-

TABLE 2
Visual Acuity Before and After Treatment

Case	Before		After	
	Right Eye	Left Eye	Right Eye	Left Eye
1	20/50	20/60	20/20	20/20
2	20/25	20/25	20/20	20/20
3	20/25	20/25	20/20	20/20
4	20/400	Counting fingers	20/400	Counting fingers
5	20/30	20/30	20/25	20/20
6	20/40	20/40	20/25	20/25
7	20/25	20/30	20/25	20/25

es.^{4,5,13} Most patients also are treated with the same immunosuppressive drugs used for juvenile idiopathic arthritis and chronic uveitis (methotrexate, azathioprine [Azasan; Salix, Raleigh, NC], or mycophenolate mofetil [CellCept; Genentech, South San Francisco, CA]), since long-term use of corticosteroids may cause serious adverse effects.^{3,5,12,19} Marked results have been achieved with canakinumab (an anti-interleukin [IL]-1 monoclonal antibody) for this disease, and variable results with anakinra (IL-1 receptor antagonist).^{20,21}

In the current case series, all patients were treated with oral prednisone and most needed at least one immunosuppressive drug to control ocular inflammation, especially methotrexate and cyclosporine. Thalidomide seems to be a promising agent for reducing granulomatous inflammation by suppressing nuclear factor kappaB activation and interference with the proliferation and differentiation of monocytes.^{3,15} Anti-tumor necrosis factor-alpha agents, such as adalimumab (Humira; AbbVie, North Chicago, IL) and infliximab, have achieved good results in some patients.⁵ However, in a study of 22 patients with BJS, most presented with persistent active disease.¹³ The results vary with immunosuppressive agents and tumor necrosis factor inhibitors, particularly regarding ocular morbidity,¹² and we used infliximab and etanercept in two refractory cases without good responses. Uveitis can be treated with steroid eye drops associated with systemic therapy.⁴ Close monitoring is important to avoid complications and decreased quality of life, since almost half of patients with BJS reported a moderate-to-severe disease effect on their lives and moderate-to-severe pain.¹³

We believe that Case 1 is the first published BJS case treated with periocular corticosteroids (peri-

ocular injection and subconjunctival implant) that had a good response and no substantial complications. We believe this kind of treatment can be helpful in patients who do not tolerate high doses of systemic steroids or have important immunosuppressive therapy side effects. In our case series, just one case did not recover good VA after a 1-year follow-up due to dense bilateral corneal band keratopathy.

Much still needs to be ascertained about BJS, such as the risk factors for severe ocular involvement and the correlations between the clinical manifestations and genetic mutations. The current study described the demographic, clinical ophthalmologic, and systemic findings and treatments in seven patients with BJS. Periocular treatment with steroid injections may be an adjuvant therapy for ocular inflammation. This syndrome may be misdiagnosed due to its rarity and similar manifestations to other diseases. Thus, ophthalmologist must be aware of the BJS manifestations, think about this diagnosis, and order a genetic test to confirm it.

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